the activation of proteases that enhance the conversion of xanthine dehydrogenase to xanthine oxidase, and mitochondrial derangements.

[0008] Solutions for preserving organs are described in U.S. Patent Nos. 4,798,824 and 4,879,283, the disclosures of which are incorporated herein in their entirety. Despite such solutions, it is believed that there remains a need for organ and tissue preserving solutions that allow for static storage and preservation, while demonstrating superior quality preservation of organ and tissue viability and function.

Summary of the Invention

[0009] The invention provides an organ and tissue preserving solution for machine perfusion preservation that demonstrates superior quality preservation when compared to existing preserving media, in terms of organ and tissue viability and function. The organ and biological tissue preservation aqueous machine perfusion solution includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties, a nitric oxide donor, and a glutathione-forming agent.

[0010] The invention also provides a preserved organ and biological tissue. The preserved organ and biological tissue includes a cadaveric organ or tissue within the machine perfusion solution in a deep hypothermic condition or a physiological condition.

[0011] The invention also provides a perfusion machine comprising a chamber that mimics a deep hypothermic environment or physiological environment, where the machine perfusion solution continuously circulates through the chamber.

[0012] The invention also provides a method for preserving an organ or biological tissue. The method includes pouring the machine perfusion solution into a chamber that mimics a deep hypothermic environment or physiological environment, circulating the machine perfusion solution continuously through the chamber, inserting a cadaveric organ or tissue into the chamber, and flushing the cadaveric organ or tissue with the machine perfusion solution.

[0013] The invention further provides a method of preparing an organ or biological tissue machine perfusion solution. This method includes providing a solution with sterile water, adding sodium gluconate, potassium phosphate, adenine, ribose, calcium chloride, pentastarch, magnesium gluconate, HEPES, glucose, mannitol, and insulin to the solution, and mixing prostaglandin E1, nitroglycerin and N-acetylcysteine into the solution.

Detailed Description of the Invention

[0014] In accordance with the present invention, the organ and biological tissue preservation aqueous machine perfusion solution includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties, a nitric oxide donor, and a glutathione-forming agent. The organ and biological tissue preservation machine perfusion solution is intended for infusion into the vasculature of cadaveric and living donor organs for transplantation. Once infused, the donor organs are exsanguinated and blood is replaced by the solution in the native vasculature of the organs to return the organs to a normothermic condition. The solution may be used under deep hypothermic conditions or physiological conditions. The solution remains in the vasculature of the organ as well as envelops the entire organ during the period of cold ischemia. This method of preservation allows for the extended storage of organs, tissues, and all biological substances. When the organ or tissue is returned to normothermic conditions, the solution is replaced with blood or other physiologic media. Variations of this solution may also be used for cold storage solution preservation. The machine perfusion solution of the invention may be used in the same manner and for the same tissues and organs as known machine perfusion solutions.

[0015] A machine perfusion solution of the invention includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties. One such prostaglandin is Prostaglandin E1 (PGE1). PGE1 is an endogenous eicosanoid of the cyclooxygenase pathway and is utilized for its potent vasodilatory properties. In addition, PGE1 has cellular and organelle membrane stabilization properties, cryoprotective properties, and ability to prevent platelet aggregation

upon the vascular endothelium post transplant. As such, PGE1 may inhibit neutrophil adhesion, inhibit neutrophil production of oxygen free radical species, counteract procoagulant activity after endothelial injury, and stabilize cell membranes. When used in vivo, PGE1 is metabolized almost instantaneously by first pass clearance through the lung, but during hypothermic conditions, PGE1 in the machine perfusion solution may remain vasoactive even after several hours.

[0016] A machine perfusion solution of the invention also contains a nitric oxide donor, such as nitroglycerin. Nitroglycerin is utilized in the solution because of its potent nitric oxide donation properties, its ability to dilate the venous vascular system and prevent vasospasm, and its ability to prevent complement activation upon transplant. Nitroglycerine is known to relax smooth muscle cells of the endothelium, scavenge free oxygen radicals during reperfusion, and prevent the production of such radicals during cold ischemia.

[0017] Compounds that form glutathione (glutathione-forming agents) are also components of a machine perfusion solution of the invention. One such compound is n-acetylcysteine. Glutathione (GSH) is synthesized from L-glutamate, L-cysteine, and glycine in 2 ATP-dependent reactions. The first reaction, known as catalyzed bygamma-glutamylcysteine synthetase, is effectively rate-limited by GSH feedback. The second involves GSH synthetase, which is not subject to feedback by GSH. When GSH is consumed and feedback inhibition is lost, availability of cysteine as a precursor becomes the rate-limiting factor. As such, N-acetylcysteine is proposed to be the only glutathione precursor that can enter the cell freely. In addition, the constitutive glutathione-building properties of N-acetylcysteine help prevent the formation of free oxygen radicals generated during the preservation period and during reperfusion with a recipient's blood.

[0018] According to a preferred embodiment of the invention, an organ and biological tissue preservation cold storage solution containing PGE1, nitroglycerin, and N-acetylcysteine in the preserving solution significantly improves vascular resistance, vascular flow, and calcium efflux during the organ preservation period. The inhibition of calcium efflux over time in kidneys